REMARKS

The Office rejected claims 27-44 under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description, and 35 U.S.C. § 103(a), for allegedly being unpatentable in view of U.S. Patent Publication 2003/0192078 (Fischhoff et al.) ("the '078 publication"), which is a divisional of U.S. Patent Application No. 08/434,105. Finally, claims 27, 30-32, 38, and 41-44 remain rejected on the ground of non-statutory obviousness-type double patenting for allegedly being unpatentable over claims 1-3 of U.S. Patent 6,833,449 ("the '449 patent"). Reconsideration is respectfully requested.

Claims 28, 29, and 33 have been amended to improve clarity without changing claim scope. It is self-evident that codons are substituted for codons in a method of making a nucleic acid that starts with a coding sequence, and not for amino acids.

I. The Rejection Under Section 112, First Paragraph, Should Be Withdrawn.

Claims 27-44 were rejected under Section 112, first paragraph, for allegedly encompassing subject matter that is not described in the specification so as to reasonably convey to one of ordinary skill that Applicants had possession of the claimed invention as of the effective filing date of the application. (Office Action, pages 3-4.) Applicants respectfully traverse.

A. The rejection of claims 27, 30-32, and 38 was improper because the bases for rejection do not apply to these claims.

The Office addressed only claims 28, 29, 33, 39, and 40 in the rejection. The bases for rejection pertain to specific claim language that is not present in claims 27, 30-32, and 38, and thus the rejection does not apply to those claims. Because no basis has been alleged for rejecting claims 27, 30-32, and 38, the rejection of these claims was improper, and should be withdrawn. (Similarly, it was improper to reject multiple dependent claims insofar as they depend from claim 38.)

B. The rejection alleging lack of written description was improper because the specification adequately describes the subject matter as claimed.

The Office rejected claims 27-44, alleging that the specification fails to support claim limitations (found in claims 28, 29, 33, 39, and 40) related to modifying codons

at the 5' end, e.g., for *at least* the first 25 or 59 amino acids, of *any* coding sequence. Applicants respectfully disagree.

The written description requirement is satisfied when persons of ordinary skill in the art can recognize from the application's disclosure that the applicants invented what is claimed. *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). As explained in detail below, one of ordinary skill (as of the priority date) would have recognized from the instant specification that, in one embodiment, the claimed method entails modifying the 5' end of any starting coding sequence to make a nucleic acid, and the modifications may include codons for *at least* the first 25 amino acids or *at least* 59 amino acids in the 5' end of a coding sequence. Thus, Section 112, first paragraph, is satisfied.

As part of the response to the Office Action, Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 from James A. Baum, Ph.D., a scientist whose long experience in the field qualifies him to comment on what one of ordinary skill in the art would have understood from the specification at the time that it was filed in 1989. (See Baum Declaration at paragraphs 1.1-1.3.)

The Office contends that the specification only supports the concept of modifying "about 25 amino acids" or "modifying 59-138 codons" of the particular *B.t.* sequence described in the Examples, not substituting "codons for at least 59 or at least the first 25 amino acids." (Office Action, page 4 (emphasis in original).) In effect, the Examiner seeks to improperly limit the disclosure to preferred embodiments described in the application. However, one of ordinary skill would have understood upon reading the specification that *additional* codon modifications beyond the first 25 or 59 amino acids (i.e., modifying *at least* the first 25 or 59 codons) were contemplated as part of the invention, and that the features of the present claims are adequately described. The application teaches that codon substitutions at the 5' end of the coding sequence, i.e., substitutions of about the first 25 codons, with plant preferred codons enhances expression of a coding sequence in plant cells. (Specification, page 13, lines 11-16; Baum Declaration, paragraphs 3.2-3.3.) In the same paragraph, Applicants explicitly teach that substituting codons in the "*remaining portion of the coding region,*" i.e., beyond the first 25 or 59 codons, might increase efficiency of expression. (Specification, page 13, lines 7-16 (emphasis added); Baum Declaration, paragraphs 3.2-3.4.) The specification's disclosure of performing substitutions of the first 25

codons, plus performing additional codon substitutions to increase efficiency of expression, conveys that substituting codons encoding *at least* the first 25 amino acids is part of the invention. (Baum Declaration, paragraph 3.4.)

The application also adequately describes a method of making a nucleic acid comprising a coding sequence for expression in plant cells wherein codons with the highest frequency of use are substituted for codons that encode *at least* 59 amino acids in the 5' end of a starting coding sequence. The specification states that substitutions in "as few as 59" codons at the 5' end of a coding sequence enhances expression efficiency. (Specification, page 13, lines 7-16; Baum Declaration, paragraph 3.5.) One of ordinary skill would understand that the invention encompassed making 59-138 substitutions at the 5' end, and also encompassed making *59 or more* substitutions (which is another way of saying "*at least* 59"), particularly given the specifications explicit teaching that modification of the "*remaining portion of the coding region*" might enhance expression. (Specification, page 13, lines 7-16 (emphasis added); Baum Declaration, paragraphs 3.2-3.5.)

The examples further convey that substituting codons in Figure 1 with the highest frequency of use for codons that encode *at least* the first 25 amino acids (or at least the first 59 amino acids) of the starting coding sequence is part of the invention. Exemplary nucleic acids are described which have substitutions of the first 59, 104, and 138 codons and display enhanced expression efficiency (see specification at, e.g., page 10, lines 3-11; and page 13, line 30, through page 17, line 25; Baum Declaration, paragraph 3.4). One of ordinary skill would have understood from the specification that the invention encompassed modifying the first 25 codons or the first 59 codons of a coding sequence, and also encompassed substituting these plant preferred codons for *more* than the first 25 or 59 codons in a starting coding sequence to enhance expression. (Baum Declaration, paragraphs 3.2-3.6.) Thus, the specification provides sufficient written description for modifying codons for *at least* the first 25 amino acids or *at least* 59 amino acids in the 5' end of a coding sequence so as to satisfy Section 112, first paragraph.

The Office acknowledges that the specification supports modifying "about 25 amino acids" or "modifying 59-138 codons" at page 13, lines 9 and 15-22. Importantly, section 112, first paragraph, does not impose an *ipsis verbis* or *in haec verba* (word-for-word) standard for written description. E.g., *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352,

1364 (Fed. Cir. 2003). To the contrary, the proper standard for assessing written description of the invention involves what a person of ordinary skill would have understood to be the invention, based on reading the application. Dr. Baum provides his analysis of what an ordinary researcher would have understood the patent application to teach, at the time that it was filed, in paragraphs 3.2-3.6 of his declaration. One of ordinary skill would have recognized that Applicants' invention included modifying codons for *at least* the first 25 amino acids or *at least* 59 amino acids at the 5' end of a starting coding sequence, which is sufficient to satisfy Section 112, first paragraph.

The Office also contends that the discussion in the specification about modifying the 5' end of a coding sequence, e.g., substituting 25 codons or 59-138 codons, at page 13, lines 7-16, is limited to a specific *B.t.* sequence used in the Examples, and that the specification does not describe modifying these codons in any coding sequence. To the contrary, one of ordinary skill would understand from the specification that the teaching to modify the 5' end of a starting coding sequence (including modifying codons for at least the first 25 or 59 amino acids) is a general teaching – not limited to a specific sequence in the Examples. The passage cited by the Office provides an analysis of the Examples, and it is clear from the language that the teachings are applicable to other coding sequences. (Baum Declaration, paragraphs 3.8-3.10 and 3.12.) For example, the passage introduces the analysis as broadly applicable, "[a]s an examination of the following Examples will reveal to one skilled in the art, the substitution of plant preferred codons in **a** plant expression cassette results in an increased level of efficiency in expression of the engineered protein." (Specification at page 13, lines 3-7 (emphasis added); Baum Declaration, paragraph 3.10.) The conclusions drawn from the Examples also are stated broadly, "this would suggest that **entire coding regions** need not be altered to gain a relatively significant increase in efficiency of expression, merely the amino-terminal end of the coding region." (Specification at page 13, lines 18-22 (emphasis added); Baum Declaration, paragraph 3.10.) One of ordinary skill would understand the context of the discussion of the "particular numbers" of codons modified to apply to any coding sequence, not merely the *B.t.* sequence used in the Examples. (Baum Declaration, paragraphs 3.8 and 3.10.)

The remainder of the specification also conveys that the teachings relating to 5' end modifications are applicable to coding sequences other than *B.t.* delta endotoxin.

Difficulty in expressing *B.t.* delta endotoxin is described as "an example" of reduced heterologous gene expression in plants, and the specification explicitly states that the invention is not limited to the single illustrative practice provided in the Examples. (Specification, page 2, lines 9-23, and page 21, lines 15-26; Baum Declaration, paragraph 3.7.) In addition, just prior to the passage cited by the Office, the specification states that, while the inventive method is described with respect to a "particular procaryotic gene," the method "is equally applicable to other procaryotic or even eukaryotic, genes which happen not to express well in plants." (Specification, page 12, lines 7-12; Baum Declaration, paragraphs 3.8-3.9.) The specification affirms that other foreign genes that comprise a large number of codons not preferentially expressed by plants are suitable for alteration in a manner similar to that described for *B.t.* (Specification, page 12, lines 16-20; Baum Declaration, paragraphs 3.8-3.9.)

Likewise, original claim 10 confirms that the invention includes modifications of the 5' end of any coding sequence. (Baum Declaration, paragraph 3.11.) Original claim 10 is directed to a transgenic plant comprising a chimeric gene coding for the expression of a foreign protein. The chimeric gene's coding sequence differs from that of the foreign gene in a segment *at the 5' end of the coding region*. The claim language is not limited to particular chimeric genes or foreign proteins, but encompasses modification of *any* starting coding sequence as part of the invention. The passages cited above and original claims provide further context for the analysis at page 13, lines 7-16, and a typical researcher would have understood that all features of the inventive method, regardless of where they are described in the application, are applicable to foreign genes other than *B.t.* delta endotoxin. (Baum Declaration, paragraphs 3.8-3.9 and 3.11-3.12.) As such, the specification provides sufficient support for modifying the 5' end (e.g., at least the first 25 or 59 codons) of any coding sequence, not just for specific sequences in the Examples.

For these reasons, the rejection of claims 27-44 under Section 112, first paragraph, should be withdrawn.

II. The Rejection Under Section 103(a) Should Be Withdrawn.

The Office rejected claims 27-44 under Section 103(a), alleging that the subject matter of these claims would have been obvious in view of the Fischhoff '078 publication. The Office contends that, in December 1986, Fischhoff reduced to practice "a

method of designing a synthetic Bacillus thuringiensis gene, said method comprising modifying the native sequence by substituting at least some of the codons in the native coding sequence with codons for the same amino acids but that have the highest frequency in plant genes, such as their Table 1." (Office Action, page 5.) The Office alleges that it would have been obvious to modify the '078 publication's method to use the highest frequency codons in instant Figure 1 because "there are a limited number of possible codon tables showing codons that have the highest frequency." (Office Action, page 5.) According to the Office, one of ordinary skill would have been motivated to modify the teachings of the '078 publication because "which codons are determined to be at the highest frequency is determined by the genes used to make the codon usage table." (Office Action, page 5.) Applicants respectfully traverse this rejection.

A. Fischhoff as prior art.

As the Examiner recognizes, the present application (Barton et al.) and an application of Fischhoff et al. (08/434,105) are commonly owned by Monsanto. The presently claimed invention of Barton et al. may fall within the scope of a more generic invention described and claimed by Fischhoff et al. Both applications were involved in an interference in which Fischhoff et al. was awarded priority.[1] Accordingly, the present applicants (Barton) acknowledge that the Fischhoff application is prior art for purposes of the subject matter defined by the interference count. However, the mere fact that Fischhoff may dominate the present application in terms of its teachings or claims[2] does not answer the question of whether the specific invention claimed in this application would have been obvious from Fischhoff. See, e.g., M.P.E.P. 2144.08, Part II ("The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994) ('The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious.')").

[1] As a procedural matter in the interference, Monsanto was required to designate which of its applicants was a prior inventor, and Monsanto designated Fischhoff et al.

[2] Nothing in this paper should be construed as an analysis of the scope of Fischhoff's invention or claims.

B. The rejection is based on a false premise that there are a limited number of possible codon tables showing codons that have the highest frequency.

A central premise of the rejection is that there are a limited number of codon tables from which a person of ordinary skill could have chosen. However, the Examiner offered no support for this assumption. As explained below, many codon tables can be made.[3]

The Office alleges that each of the "limited number of possible codon tables" would have been obvious over all of the others in the absence of unexpected results. In essence, this amounts to an "obvious to try" rejection, but with many possible codon tables, the facts do not warrant a rejection based on "obvious to try." The Supreme Court (in *KSR Int'l v. Teleflex*, 550 U.S. 398 (2007)) suggested that "obvious to try" might support a conclusion of obviousness when choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success, and it is clear from the facts of *KSR* that the term "finite" described a situation with very few choices. Clearly, that is not the case here.

According to the Office, one of ordinary skill would have been motivated to modify the teachings of the '078 publication because "which codons are determined to be at the highest frequency is determined by the genes used to make the codon usage table." (Office Action, page 5.) The Office has a burden of establishing obviousness, and observations about how codon frequency tables *would have been constructed* do not establish that a "limited number" of codon tables were possible. Even in 1989, there would have been numerous combinations of gene sequences from which a person could select, and sequencing technologies would have permitted a person to sequence nucleic acid from organisms to identify additional gene sequences. Factors such as the choice of genomes (organisms) to include, the choice of types of proteins to include, choice of tissues within an organism, and

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[3] One possible way to calculate the theoretical number of codon tables is to multiply the number of codon choices for each amino acid. For example, referring to the first two amino acids in the codon table of Barton's Figure 1, there are four codons for Gly (GGG, GGA, GGT, GGC) and two codons for Glu (GAG, GAA). Thus, focusing only on these two amino acids, there are 4 x 2 = 8 different permutations for codons that could be selected for the dipeptide Gly Glu (GGGGAG; GGGGAA; GGAGAG; GGAGAA; GGTGAG; GGTGAA; GGCGAG; GGCGAA). Performing this analysis for all twenty amino acids, the analysis is as follows: three amino acids have six codons each; five amino acids have for codons each; one amino acid has three codons; nine amino acids have two codons each; and two amino acids have a single codon. Therefore, the number of possible "most preferred" codon tables is calculated by the formula:
6 x 6 x 6 x 4 x 4 x 4 x 4 x 4 x 3 x 2 x 2 x 2 x 2 x 2 x 2 x 2 x 2 x 2 x 1 x 1 = 339,738,624

so on would influence the ultimate combination of genes, which in turn would influence the resultant codon table. The Office Action does not contain any reasoning or analysis that would define the possible number of codon tables, or establish that the number was "limited" in a way that was significant for purposes of 35 U.S.C. § 103, or establish why Barton's Figure 1 codon table would have been obvious.

Even if the number of codon tables was "limited," such a finding does not establish that the present invention, which uses a specific codon table, was obvious:

> Consider the size of the prior art genus, bearing in mind that size alone cannot support an obviousness rejection. See, e.g., *Baird*, 16 F.3d at 383, 29 USPQ2d at 1552 (observing that "it is not the mere number of compounds in this limited class which is significant here but, rather, the total circumstances involved"). There is no absolute correlation between the size of the prior art genus and a conclusion of obviousness. Id. Thus, the mere fact that a prior art genus contains a small number of members does not create a per se rule of obviousness.
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> M.P.E.P. § 2144.08, Part II.A.4(a).As discussed in the next section, irrespective of the size of the genus of codon tables, the present invention, directed to a method which uses the specific codon table in Barton Figure 1, was not obvious.

C. The rejection is improper because the codon table in Figure 1 was not disclosed or suggested by the cited art.

An element of every obviousness analysis is identifying differences between the prior art and the claimed invention, and one such difference is the codon table in Barton Figure 1, referenced in the claims. The Office has not identified the Barton Figure 1 codon table in a prior art reference.

In *Baird*, cited above and in the M.P.E.P., the Office rejected a claim directed to three chemical compounds under Section 103 in view of a prior art reference disclosing a generic formula encompassing a vast number of chemical compounds (including the three claimed compounds) and a few species falling within the scope of the generic formula. *Id.* at 381-383. The Federal Circuit found the claim to the undisclosed species to be patentable over the prior art reference, stating "[a] disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference

leading away from the claimed compounds." *Id.* at 383. Here, Barton's Figure 1 codon table is an undisclosed species, and the claimed method of using it is unobvious.

According to the Office, one of ordinary skill would have been motivated to modify the teachings of the '078 publication because "which codons are determined to be at the highest frequency is determined by the genes used to make the codon usage table." (Office Action, page 5.) Assuming that this statement is true, it still does not establish that the Applicant's codon table, or the claimed invention (a method that makes use of Applicant's codon table in a specific way), is obvious. Clearly missing from the Examiner's rejection is any nexus between the Examiner's general observation of how codon frequency tables are made, and why it would have been obvious to arrive at Applicant's specific codon table. The Office has failed to establish that the *particular genes* used by the present inventors would have been an obvious set of genes to use, or that the codon usage table of Figure 1 would have been an obvious result from any set of genes suggested by the prior art. There is insufficient connection between the Office's abstract observation about how codon tables are made and the specific limitations of the claims.

Thus, the subject matter of claims 27-44 is patentable over the disclosure of the '078 publication, and the rejection under Section 103 should be withdrawn.

III. The Rejection Alleging Non-Statutory Obviousness-Type Double Patenting Should Be Withdrawn.

The Office rejected claims 27, 30-32, 38, and 41-44 for non-statutory obviousness-type double patenting, citing claims 1-3 of the '449 patent. Claims 1-3 of the '449 patent are directed to nucleic acids encoding a toxic portion of Cry1A, wherein codons of the nucleic acid are selected from codons described in Figure 1 as being used at the highest frequency in plants. The Office contends that "a product in which each codon is a codon in Fig 1 used at the highest frequency [] makes obvious [a] method of making the product by modifying the coding sequence substituting the native codons for the codons in Fig 1 used at the highest frequency." (Office Action, page 7.) Applicants respectfully traverse the rejection.

The rejection is deficient because (1) the Office failed to articulate *why* the nucleic acid claimed in the cited patent anticipates or renders obvious the method of the present claims and (2) the Office inappropriately uses the *disclosure* of the '449 patent claims

as prior art in forming the rejection. Patent Office guidelines require an obviousness-type double patenting rejection to clearly set forth the reasons why a person of ordinary skill would conclude that the claimed invention would have been an obvious variation of the invention defined in a patent claim. M.P.E.P § 804. Here, the Office merely asserts that the claimed invention is obvious, without providing reasoning as to how a nucleic acid product suggests a particular way of selecting a nucleic acid sequence or method of making the nucleic acid.

Furthermore, the Office inappropriately based the rejection on what is *disclosed* by the claims of the '449 patent, rather than what is *defined* by the claims. See *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1280-81 (Fed. Cir. 1992) ("Our precedent makes clear that the *disclosure* of a patent cited in support of a double patenting rejection cannot be used as though it were prior art, *even where the disclosure is found in the claims*." (emphasis in original)). The words of a claim are considered only to determine the defined *invention*, which then is compared to the *invention* defined by the pending claims. The invention of claims 1-3 of the '449 patent is a nucleic acid (i) encoding a toxic portion of a Cry1A protein and (ii) comprising particular codons. A nucleic acid product does not generally teach or suggest the method by which its sequence was selected or the method by which it was made.

The following example is illustrative of the proper approach for analyzing this double patenting question. The claims of the '499 patent are directed to a nucleic acid. A nucleic acid is a chemical substance, but it can be represented by its chemical formula, such as the nucleotide sequence that begins: cc atg gac aac aac cca aac atc aac gag tgc atc cca tac aac tgc .... (See the beginning of SEQ ID NO: 1 of the '449 patent.) It is possible to determine chemical properties of the nucleic acid, such as its sequence and length; and it is possible to deduce other properties, such as deducing from the nucleotide sequence whether the nucleic acid encodes an amino acid sequence. However, it is not possible (or at least not obvious) how to determine, from the nucleic acid or its sequence, the process by which a scientist selected the nucleotide sequence. In order to decipher the process, it is necessary to look beyond the chemical (the nucleic acid claimed in the '449 patent), and instead look to the disclosure of the '449 patent. Whether that disclosure is found in the summary, the detailed description, the claims, the figures, or some combination thereof, the law is clear that

the disclosure is off-limits for the double patenting analysis. The observation that the claims "refer to making the sequence by selecting from the codons in Figure 1 used at the highest frequency" (Office Action, page 6) is an observation about the disclosure of the '449 patent, not an observation about what would have been obvious from the nucleic acid that was claimed.

The rejection of claims 27, 30-32, 38, and 41-44 for non-statutory obviousness-type double patenting should be withdrawn.

IV. Conclusion

In view of the above amendment, Applicants believe that the pending application is in condition for allowance. The Examiner is invited to contact the undersigned attorney by telephone if there are issues or questions that might be efficiently resolved in that manner.

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